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Plasma cortisol and oxytocin levels predict help-seeking intentions for depressive symptoms

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Abstract

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Keywords

cortisol, oxytocin, levels, plasma, predict, depressive, help-seeking, symptoms, intentions

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Methods: Morning plasma cortisol and oxytocin levels, psychopathology, suicidal ideation, help-seeking intentions from informal sources including family and friends, and formal sources including health professionals, and perceived social support were quantified in 63 adults meeting DSM-5 criteria for major depressive disorder (MDD) who were not receiving any treatment, and 60 healthy controls. Between-group analyses of variance, correlations, and hierarchical multiple regressions were employed.

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Conclusions: Neuroendocrine changes associated with depression may contribute to low help-seeking from friends and family, which may have implications for interpersonal support and outcomes. Research and clinical approaches which incorporate biological as well as

psychosocial factors may allow for more targeted and effective early interventions to address lack of help-seeking and depression progression.

1. Introduction

Depressive disorders and suicide are leading causes of morbidity worldwide, and their magnitude is increasing (Whiteford et al., 2013). Early treatment reduces long term impairment and is cost effective (Chisholm et al., 2004), however, large scale research spanning numerous countries and including thousands of participants shows that most people with major depressive disorder (MDD) do not receive treatment, even where effective treatments are available (Kocsis et al., 2008; Thornicroft et al., 2017). Reasons for the under-treatment of depression are multi-factorial, however a major contributing factor is a widespread reluctance of affected people to seek help (Kocsis et al., 2008; Thornicroft et al., 2017). This refusal of, or withdrawal from, help has been termed *help-negation* (Clark and Fawcett, 1992; Rudd et al., 1995) and is considered the most difficult barrier to the treatment of depression (Han et al., 2006).

Previous research differentiates between help-seeking from informal sources including friends and family, and formal sources including health care professionals and helplines. Most previous studies of help-seeking for mental health problems have involved sub-clinical student populations, who prefer seeking informal rather than formal help (Thomas et al., 2014). A large-scale epidemiological study also found a general preference for informal sources of help, and that the presence of depressive symptoms was associated with lower intentions to seek help from family and friends, but no differences in formal help-seeking intentions (Chin et al., 2015). It is important to consider informal supports, because friends and family often facilitate treatment uptake and adherence in those with depressive symptoms (Chin et al., 2015; Lindsey et al., 2010), and are important points of intervention in suicidal behaviour (Barnes et al., 2002).

It has traditionally been assumed that psychosocial factors underlie the widespread reluctance of people to seek help for depression, and much research has examined the contributions of factors such as stigma or embarrassment, however these seem to be only weakly negatively associated with help-seeking (Clement et al., 2015). There is no clear evidence to demonstrate that campaigns to increase treatment uptake through targeting stigma are successful (Dumesnil and Verger, 2009; Henderson et al., 2013). Additionally, somewhat counterintuitively, avoidance of treatment for depressive symptoms and psychological distress is greater in individuals with greater psychopathology, stress levels, and suicidal ideation (e.g. Carlton and Deane, 2000; Rudd et al., 1995; Sawyer et al., 2012). These factors lead us to propose that help-negation might be related to biological, particularly neuroendocrine, changes associated with the onset or progress of depression itself, which may be linked to interpersonal difficulties and social withdrawal. To date there has been little examination of relationships between help-seeking intentions, psychopathology and biological factors. Overlooking the contribution of biological factors to help-negation may account for the sub-optimal success of treatment uptake campaigns targeting psychosocial factors, and further research is needed.

Cortisol, an output of the hypothalamus-pituitary-adrenal (HPA) axis, is a consistent neurobiological indicator of stress, anxiety and depression (Levine et al., 2007). Prolonged HPA hyperactivity through chronic stress is related to cognitive impairment (Lupien et al., 2009), social withdrawal behaviour (Tops et al., 2005) and mood changes (Sapolsky, 2000). Excess cortisol is a risk factor for developing MDD, and those with MDD often have disturbances in diurnal cortisol rhythms, increased resistance to the feedback action of glucocorticoids, higher basal levels and cortisol awakening response (Herbert, 2013). There are indications that individuals with higher basal cortisol display both reduced closeness and

that others desire to be less close to them (Ketay et al., 2017). Individuals with severe MDD often show increased HPA-axis activity, which normalises during successful antidepressant pharmacotherapy (Barden et al., 1995). Anti-depressants might elevate mood in MDD through their long-term effects on HPA regulation (Barden et al., 1995). Depression-like withdrawal and immobility can be induced in laboratory animals (Kulkarni and Dhir, 2007), indicating that it can occur without language-based cognition, which implies a role for physiological processes. Vegetative symptoms in depression may stem from processes that evolved to preserve energy during insurmountable stress (Gilbert, 2001; Hart, 1988; Tsiouris, 2005). When placed in stressful situations from which escape is not possible, animals will initially struggle and try to escape, but eventually develop immobility, a failure to persist in active forms of coping with stressful stimuli. This passive behaviour is termed behavioural despair, which is believed to be equivalent to depression (Porsolt et al., 1977), and it is reversed with selective-serotonin reuptake inhibitors and with tricyclic antidepressants (Kulkarni and Dhir, 2007). Cortisol levels may therefore be related to help-negation and to depressive symptoms including vegetative symptoms, social withdrawal and cognitive impairment. Relationships between cortisol levels, help-negation and symptom severity are not yet known.

Oxytocin is a hormone which mediates a range of complex social behaviours relevant to group-living mammals, including attachment, trust, and social support-seeking and in some circumstances aggression (Heinrichs et al., 2009; Smith et al., 2017). Oxytocin is also implicated in depression (Viero et al., 2010). It may therefore help to explain help-negation as symptoms worsen in MDD. Oxytocin is a nonapeptide hormone which is synthesised in hypothalamic nuclei and released directly into the bloodstream from axon terminals in the posterior pituitary (MacDonald and MacDonald, 2010). Oxytocin is also transported from the

hypothalamus to key brain areas, where it acts as a neurotransmitter (MacDonald and MacDonald, 2010). Central effects of oxytocin include inhibition of stress-induced hypothalamus-pituitary-adrenal (HPA) axis responsiveness, promotion of social behaviours, and anti-depressant effects (Scantamburlo et al., 2007). Oxytocin is implicated in numerous psychopathologies characterised by social discomfort, including depression, anxiety and psychoses (Viero et al., 2010). Some symptoms of depression (social withdrawal, reduced eye contact and low libido) may reflect blunted oxytocin function (Neumann, 2008). Help-seeking, particularly informally, usually involves interpersonal exchanges. Because oxytocin is often inversely related to depressive symptoms, anxiety and stress (Scantamburlo et al., 2007), and modulates social withdrawal and stress coping (Pompili et al., 2010), oxytocin abnormalities may be related to help-negation in MDD. This possibility has yet to be examined.

Given the clear involvement of biological processes in depression and withdrawal behaviour, it is of interest to investigate their role in help-seeking intentions. Both cortisol and oxytocin may represent modifiable risk factors for help-negation which potentially could be targeted in novel interventions. The current study examined biological processes in connection with symptom severity and help-seeking intentions in depressed and healthy individuals.
Based on previous research, it was predicted that:

1. Help-seeking intentions, particularly from informal sources, would be lower in participants with MDD than healthy controls.
2. Cortisol will be negatively related to help-seeking intentions and perceived social support and positively related to psychopathology, and the opposite patterns would be observed for oxytocin.
3. Cortisol and oxytocin levels would be more closely related to informal than formal

help-seeking intentions, as these involve more socially based interpersonal interactions.

4. Cortisol and oxytocin would both uniquely predict variance in help-seeking intentions, after accounting for levels of psychopathology and perceived social support.

2. Methods

2.1 Participants

The protocol was approved by the local ethics committee, and all participants gave informed written consent. Sixty-three adults were recruited who met the DSM-5 diagnostic criteria for MDD, were not currently receiving treatment and had not recently had any treatment, along with 60 healthy controls. Participants were recruited through advertisements in local media and notices at the university. Exclusion criteria across groups included neurological disorders, substance use disorders, and use of corticosteroid medication. Participants were screened prior to the study with regard to exclusion criteria, and to ensure that depressed participants likely met DSM-5 criteria for MDD and healthy controls had no significant mental health problems. Depressed participants were also interviewed by a clinical psychologist on arrival at the clinical trials unit to confirm that they met DSM-5 diagnostic criteria for major depressive disorder, using the Mini International Neuropsychiatric Interview (Lecrubier et al., 1997), and to ascertain treatment history and reasons for not being in treatment. Participants received a store voucher of small value as a reimbursement for their time and inconvenience.

2.2 Measures

All participants completed the following measures: The Depression, Anxiety and Stress Scales-21 (Lovibond and Lovibond, 1995), an overall measure of psychological distress incorporating *Depression*, *Anxiety* and *Stress* subscales. The General Help-Seeking Questionnaire-Vignette version (Wilson et al., 2005), a measure of intentions to seek help in the event of mental health problems. Participants indicate on a 7-point Likert scale how likely

they would be to seek help for depressive symptoms from specific informal (e.g. friends, family, partner) and formal (e.g. doctor, psychologist, helpline) sources if they were experiencing the same problems as the person in the vignette (1= *Extremely unlikely*, 3 = *Unlikely*, 5 = *Likely*, 7 = *Extremely likely*). The Interpersonal Support Evaluation List-12 (Cohen et al., 1985), which yields a total score measuring perceived social support, and three subscales reflecting perceived availability of *Appraisal* (advice or guidance), *Belonging* (empathy, acceptance, concern), and *Tangible* social support (help or assistance, including material and financial aid). The Brief Symptom Inventory (Derogatis and Melisaratos, 1983) quantifies somatic and psychological symptoms of all major mental disorders. For this study we used Item 9 "*thoughts of ending own life"* as a measure of suicidal ideation over the past week. Additional psychometric and biometric measurements were also collected as part of a larger study of MDD.

2.3 Blood collection and processing

Venepuncture occurred between 9-11 am. Blood (8mL) was collected from a vein in the cubital fossa into tubes with EDTA then immediately placed on ice. Aprotinin was added (25µL/mL blood) within 5 minutes of collection. Within 20 minutes of collection, blood was centrifuged at 2800rpm and 4oC for 10 minutes, and then plasma was aliquoted and stored at -80oC until analysis. Plasma cortisol and oxytocin were measured using a standard ELISA method with detection at 450nm. Samples and standards were run in triplicate. The cortisol assay had a sensitivity of 2.44 ng/mL with intra-assay and inter-assay variance of less than 9% and 10%, respectively. The oxytocin assay had a sensitivity of 15pg/mL with intra-assay and inter-assay variance of less than 14% and 17%, respectively.

2.4 Statistical analyses

A chi square test was used to compare sex distributions in the MDD versus healthy control groups. Prior to analysis, data were examined for outliers and deviations from normality. To correct for skew, the DASS, ISEL and BSI data were log transformed and analyses were performed on both the untransformed and transformed data. The results were found to be the same; hence only the untransformed data are reported. Prior to analyses, raw cortisol and oxytocin values were log transformed to better approximate normal distributions. Two-way Group (MDD, control) by Sex (male, female) ANOVAs were used to compare the effects and interactions of clinical status and sex on each study variable. Pearson correlations were used to assess relationships between the variables. Hierarchical multiple regressions were employed to investigate whether cortisol and oxytocin accounted for unique variance in help-seeking intentions beyond that explained by symptom severity and psychosocial variables.

3. Results

3.1 Participant characteristics and psychometrics

Table 1 shows participant characteristics. Venepuncture was unsuccessful for two participants and another participant did not complete all questionnaires, resulting in complete data sets for 60 controls and 60 participants with MDD. The groups did not differ significantly on age. There were 35 females in each group, 25 males in the control group and 28 males in the depressed group. The distribution of sexes between the groups was not statistically significant X^2 (2, N = 123) = 0.1, p = .76. Two-way ANOVAs with diagnostic Group (MDD, control) and Sex (female, male) as between-group factors indicated that there were no significant differences between males and females, and no Sex by Group interactions for any of the study variables (P>.05 in all cases), hence all further analyses were run with data from both sexes

combined.

Participants with MDD had higher cortisol, lower oxytocin, and higher psychopathology (DASS total, Depression, Anxiety and Stress) than controls (Table 1). Help-seeking intentions were significantly lower in the MDD than control groups for informal sources and overall, but did not differ significantly between groups for formal sources of help. Perceived social support (ISEL-12) did not differ significantly between groups. Suicidal ideation (BSI Item 9) was higher in the MDD than control groups.

Table 2 shows rank-ordered reasons given by depressed participants for not being in treatment for their current MDD. The most commonly reported reasons were "side effects of medication" and "unsure/ don't know".

3.2 Correlational analyses

Correlations between variables are shown in Table 3. Cortisol correlated positively with psychopathology (DASS Total) and suicidal ideation (BSI Item 9) and negatively with help-seeking intentions from informal sources, and overall help-seeking intentions (GHSQ). Oxytocin correlated positively with GHSQ help-seeking intentions from informal and all sources overall. Psychopathology correlated with suicidal ideation and lower help-seeking intentions from informal and overall sources. Help-seeking intentions from informal sources correlated positively with perceived social support (ISEL-12) and inversely with suicidal ideation. Help-seeking from formal sources correlated only with overall help-seeking intentions. Overall help-seeking intentions correlated positively with perceived social support and inversely with suicidal ideation. Perceived social support also correlated inversely with suicidal ideation. The pattern of correlations between help-seeking intentions and other measures was similar at the single item level to the subscale level, with no types of formal

help (internet, telephone or face-to-face modes) correlating with hormones, and all types of informal help (friends, relatives, partner) correlating with hormones. Therefore the results are reported at the subscale rather than single-item level.

3.3 Hierarchical multiple regression

A hierarchical multiple regression was employed to investigate whether cortisol and oxytocin accounted for unique variance in informal help-seeking intentions beyond that explained by psychopathology (DASS Total and BSI suicidal ideation) and perceived social support (ISEL-12; Table 4). Because help-seeking intentions from formal sources did not correlate significantly with any other key study measures, a regression analysis was not performed for formal help-seeking intentions. Also, while overall help-seeking intentions correlated with cortisol and oxytocin levels, because only the informal help-seeking subscale was correlated with hormonal measures, we did not perform a regression to investigate the value of hormones in predicting overall help-seeking intentions.

For the regression analysis, psychopathology (DASS total), perceived social support (ISEL-12) and suicidal ideation (BSI Item 9) were entered into the first step as control variables, then cortisol and oxytocin levels were entered into the second step. In the first model which included psychopathology, suicidal ideation and perceived social support, only psychopathology (DASS; β = -.35, p <.001) emerged as a significant predictor of intentions to seek informal help. When cortisol and oxytocin were entered into the second step of the regression, both emerged as significant predictors of intentions to seek informal help, (β = -.24, p =.01 and β = .21, p =.01, respectively) and psychopathology (DASS) was no longer a significant independent predictor of informal help-seeking intentions. Overall, the second

regression model was significant and accounted for 30% of the variance in intentions to seek informal help, $F = 9.68$, $p < .001$, $R^2 = .30$ (Table 4).

4. Discussion

We investigated whether biological factors are associated with the widespread avoidance of help and treatment observed in depression. This represents a novel approach because previous studies that have sought to understand help-negation for mental health problems have concentrated on psychosocial issues and largely overlooked the possible role of biological pathways in avoidance and withdrawal from help and treatment in MDD.

The hypothesis that help-seeking intentions, particularly from informal sources, would be lower in participants with MDD than healthy controls was supported. Additionaly, the severity of psychopathology and suicidal ideation correlated negatively with informal and overall help-seeking intentions. These results are consistent with previous studies which have found help-seeking intentions to be inversely related to the severity of mental health problems, consistent with a help-negation effect (e.g. Carlton and Deane, 2000; Rudd et al., 1995; Sawyer et al., 2012). As in previous studies, we found important distinctions between help-seeking intentions from formal versus informal sources. Participants with MDD had lower intentions than controls to seek help from informal sources, however there were no between-group differences for formal help-seeking intentions, with mean responses in both groups being mid-range between *unlikely* and *likely* for intentions to seek help. Our findings with a clinically depressed sample are similar to previous ones in subclinical populations which showed that the help-negation effect does not seem to apply strongly to formal sources of help (Frost et al., 2017; Yakunina et al., 2010). Our results are also consistent with previous evidence that depressive symptoms are associated with lower intentions to seek help

from family and friends, but no effect on intentions to seek help from healthcare professionals (Chin et al., 2015). Chin et al.(2015) interpreted their results in psychosocial terms, that a depressed mood and negative thinking may make individuals reluctant to share their problems with family and friends as they may feel burdensome or pessimistic.

In the current study we looked beyond psychosocial factors to investigate the novel hypothesis that help-negation is related to neuroendocrine changes associated with depression. Specifically, we predicted that cortisol would be positively related to psychopathology and suicidal ideation and negatively related to perceived social support and help-seeking intentions, and the opposite pattern would be observed for oxytocin. This hypothesis was partially supported, as overall and informal help-seeking intentions were related to these neuroendocrine markers, psychopathology, suicidal ideation and perceived social support in the predicted directions. Our results indicated that cortisol was positively associated with symptom severity and suicidal ideation and negatively associated with help-seeking intentions. This pattern of results indicates that cortisol may be a common factor contributing to the help-negation effect, that is higher psychopathology and suicidal ideation being related to lower help-seeking intentions, found in this and previous studies (e.g. Clark and Fawcett, 1992; Rudd et al., 1995). Participants with MDD had higher mean morning cortisol levels than control participants, consistent with previous research indicating involvement of the HPA-axis in depression (Herbert, 2013). The correlation between suicidal ideation and cortisol is consistent with studies which have found that disturbances in HPA-axis function and cortisol are linked to suicide (Jokinen and Nordström, 2009).

In our study, participants with MDD had lower oxytocin levels compared to controls. Similar findings have been reported previously in small samples of depressed females (Ozsoy et al., 2009; Yuen et al., 2014). Overall, however, very few previous studies have examined

oxytocin levels in MDD versus healthy controls, and findings are inconsistent (Massey et al., 2016). This may be due to small sample sizes, heterogeneity in study designs, and other methodological limitations (Massey et al., 2016). The current results suggest a need for further research into relationships between depressive symptoms and oxytocin. Higher oxytocin levels were associated with greater intentions to seek help from informal sources for depressive symptoms. Additionally, perceived social support was positively correlated with help-seeking from informal sources, indicating that those who expressed higher help-seeking intentions from informal sources tended to perceive closer interpersonal bonds with friends and family, as well as having higher oxytocin levels. Animal research indicates that oxytocin plays key roles both in pro-social and anti-social behaviour (Smith et al., 2017). Oxytocin buffers stress in the context of social behaviour, decreasing anxiety and helping animals to overcome their natural avoidance of proximity, inhibiting defensive behaviour, and facilitating approach behaviour (reviewed in Heinrichs et al., 2009). The current results indicate that impairment in the oxytocinergic system in depression may be related to both interpersonal difficulties and reduced help-seeking from friends and family.

The hypothesis that cortisol and oxytocin levels would be more closely related to informal than formal help-seeking intentions was also supported, with only informal help-seeking intentions correlating with neuroendocrine and psychosocial variables. Our results provide novel evidence for separate processes being involved in informal versus formal help-seeking, with the former being an interpersonal process related to psychosocial and neuroendocrine function. Social and emotional difficulties are closely interwoven in depression (Rottenberg and Gotlib, 2004). Stressful interpersonal relationships are risk factors for depression (Joiner, 2014), and in turn those providing informal support can become frustrated with the depressed individual and reject them (Rottenberg and Gotlib, 2004). Interpersonal therapy (IPT) is

efficacious in reducing depressive symptoms through improving depressed individuals' social functioning, however the mechanisms through which it brings about changes remain largely unknown (Rottenberg and Gotlib, 2004). The current results for help-seeking and perceived social support, in the context of previous psychosocial literature, lead to the suggestion that lower intentions to approach friends and family for help in MDD are related to interpersonal difficulties observed in depression and that both may be underpinned by neuroendocrine pathways which are involved in depression, stress and affiliation, modulated in part by cortisol and oxytocin.

We also predicted that cortisol and oxytocin would both uniquely predict variance in help-seeking intentions after accounting for levels of psychopathology and perceived social support. This hypothesis was supported for informal help-seeking intentions only, with both oxytocin and cortisol levels being statistically significant unique contributors to help-seeking intentions from informal sources, after accounting for symptom severity, perceived social support and suicidal ideation. This provides the first evidence, to our knowledge, of neuroendocrine involvement in predicting mental health help-seeking.

Cortisol and oxytocin did not correlate with each other, but were independently correlated with other psychosocial variables and uniquely predicted help-seeking intentions. Previous studies show variability in the correlation between oxytocin and cortisol across populations, and laboratory tasks (Brown et al., 2016). Previous research indicates that oxytocin and cortisol may correlate with psychometric measures independently, but not with each other (Gordon et al., 2008). This has been interpreted to indicate that complex social behaviour is shaped by both neuro-endocrine systems, with each independently predicting different

psychosocial measures (Feldman et al., 2007; Gordon et al., 2008).

The current results did not differ between males and females. Previous neuroendocrine research often has uneven sex ratios (MacDonald and MacDonald, 2010), and while some cortisol and oxytocin studies show sex effects or interactions, these are inconsistent (MacDonald and MacDonald, 2010; Young and Korszun, 2010). A meta-analysis of cortisol in MDD concluded that depression seems to elevate cortisol levels equally in men and women (Stetler and Miller, 2011), consistent with our results. Females are more likely to experience MDD than males (Angst et al., 2002; Kessler, 2003). The extent to which this is related to biological vulnerabilities versus gender-related environments is unclear (Kessler, 2003). Formal treatment-seeking is higher in females than males (Angst et al., 2002), however our sample excluded people who were receiving or seeking any treatment and thus may have been more homogeneous in this respect. Informal help-seeking levels may be similar between males and females (Angst et al., 2002). Overall our results suggest an equivalent role of cortisol and oxytocin in predicting help-seeking intentions for depressive symptoms in both sexes.

While the neuroendocrine biomarkers provide some insight into biological pathways associated with help-negation, we found no correlations between help-seeing intentions from formal sources including health care professionals, and symptom severity, or psychosocial or biological variables. Further, when participants with MDD were asked why they were not seeking treatment, the most frequently given reasons were *concerns about side effects of medication* or simply *unsure/ no reason*. We found little evidence of stigma being a barrier to seeking professional treatment in the current sample. While the neuroendocrine results apply only to informal help-seeking, they may still have implications for treatment uptake,

adherence and outcomes in MDD. Help-seeking is not an isolated, rational action, but a process which involves influence from individuals' social network including friends and family (Lindsey et al., 2010). Informal supports may help to confirm the presence of a problem and influence help-seeking behaviour and recovery by providing emotional support, reminding and helping the depressed person to attend appointments, and promoting adherence to treatment (Chin et al., 2015; Lindsey et al., 2010). Informal sources of help have been recognised as important gateways to treatment for mental health problems, and important points of intervention in suicidal behaviour (Barnes et al., 2002). Our results are therefore potentially clinically relevant and indicate a need for increased awareness of the role of biological factors in withdrawal from informal support in depression, which may have downstream effects on formal help-seeking.

The results of this study have implications for understanding depressive disorders, which represent a large burden of untreated illness. Help-negation in MDD is a process associated with poorer outcomes, long term impairment and suicide risk (Stanley et al., 2015).This study provides preliminary evidence to support the development of a biopsychosocial model to better understand the widespread reluctance of depressed individuals to seek help and treatment. It is hoped that developing more comprehensive models to incorporate biological processes including those mediated by oxytocin and cortisol may lead to novel interventions which could reduce transitions to social withdrawal and suicidal behaviours in high risk individuals.

If the widespread avoidance of help and withdrawal from family and friends in MDD can be understood as a commonly occurring response to chronic stress and associated neuroendocrine changes in MDD, it may facilitate problem-solving. There is some evidence

that education about biological aetiological factors of depression is associated with increased empowerment, motivation and preference for treatment, and decreased stigma (Goldstein and Rosselli, 2003). Additionally, biological education about depression significantly increases willingness to seek help, but de-stigmatisation education does not (Han et al., 2006). This is possibly because biological education legitimises depression as a disease entity, which increases motivation to solve the problem. Destigmatisation, on the other hand, reduces people's negative appraisals of the depressed individuals, but may not increase people's motivation to seek help (Han et al., 2006). Our results also suggest that iatrogenic concerns may deserve more direct attention as barriers to seeking treatment for MDD.

Further research is needed to determine whether oxytocin administration might offer an adjunctive treatment along the pathway between HPA axis activation, depressive symptoms and withdrawal from help. Previous research indicates that social support and intranasal oxytocin both show stress reduction and anxiolytic effects, which are stronger when combined (Heinrichs et al., 2003). There have been no long term randomised controlled trials (RCTs) of oxytocin administration in MDD. Given the evidence for the involvement of oxytocin in the stress response, mood and interpersonal function, there is a need for RCTs of oxytocin as an adjunctive treatment in MDD (Cochran et al., 2013).

4.1 Limitations and future directions

We analysed data at a single time point only, and further, longitudinal, studies are needed to better understand the role of the HPA axis function in this context, and to determine causal relationships between the variables. We quantified only two hormones and there are likely to be complex interactions with other neurobiological pathways in depression that warrant

further investigation. However, is a strength of the study that we employed a multi-systems approach, examining markers of two endocrine systems in relation to psychosocial responding, because multi-systems approaches may aid the construction of more meaningful and complete models of biological systems involved in mental and physical health (Laurent et al., 2016). Future research is needed to determine whether interventions aimed at changing oxytocin or cortisol levels will have a positive effect on interpersonal relationships in people with MDD and their help-seeking intentions. Although we included a measure of perceived social support, it would also be of interest to examine other measures of interpersonal functioning in relation to help-seeking and hormones. Finally, we measured help-seeking intentions rather than actual help-seeking behaviours. Previous research indicates that the two are correlated (e.g. Wilson et al., 2005), however intentions differ from actual help-seeking behaviour, so further assessment of behaviours would be useful.

4.2 Conclusions

The results provide new information about interactions of psychosocial and neurobiological factors which may help to explain why those with depressive symptoms are often reluctant to seek help. More specifically, they indicate that help-seeking intentions from friends and family are related to cortisol and oxytocin levels, symptom severity and perceived social support, with the strongest predictors being cortisol and oxytocin. Lower help-seeking intentions in MDD may be related to HPA axis activity, and dysfunctions in oxytocin metabolism associated with depression. Further research is needed to ascertain whether interventions aimed at changing hormone levels can improve interpersonal difficulties in MDD. In the meantime, education regarding the involvement of biological factors in reluctance to seek help for depressive symptoms and the importance of social support could form the basis for new approaches to help and engage individuals with MDD, which go beyond traditional psychosocial factors.

Tables

Table 1

Descriptive data and analyses of variance between depressed and healthy controls for demographic, hormonal and psychometric study variables.

		Depressed	Control		
Variable		Mean (SD)	Mean (SD)	*F*	*p*
Age	Years	31.9 (14.55)	31.83 (10.98)	0.001	0.976
Cortisol	nmol/L	252.29 (102.63)	106.65 (64.53)	86.98	<.0001
Oxytocin	pg/mL	158 (140)	261.7 (158.97)	14.68	<.0001
Psychopathology $_{DASS}$	Total	58.7 (26.51)	21 (18.32)	83.38	<.0001
	Depression	23.21 (9.38)	6.2 (7.41)	123.76	<.0001
	Anxiety	13.59 (10.65)	4.50 (5.57)	34.68	<.0001
	Stress	21.90 (9.6)	10.30(7.97)	52.95	<.0001
Help-seeking intentions $_{GHSQ}$	Informal	2.94(1.29)	4.5(1.44)	39.97	<.0001
	Formal	3.51(1.51)	3.41(1.32)	0.15	0.7
	All sources	3.02 (.96)	3.64(.96)	12.57	0.001
Social support $_{ISEL-12}$	Total	28.95(7.14)	29.28 (2.52)	0.12	0.74
Suicidal Ideation $_{BSI}$	Item 9	.76 (1.12)	.13 (.50)	15.91	<.0001

Note: DASS= Depression, Anxiety and Stress Scales; GHSQ = General Help-Seeking Questionnaire; ISEL-12 = Interpersonal Support Evaluation List-12; BSI =Brief Symptom Inventory.

Table 2

Rank- ordered reasons given by depressed participants for not seeking treatment.

Self-reported reasons by depressed participants for not seeking treatment	*n* (%)
Previously had side effects from medication	15 (24)
Not sure/ no reason	14 (22)
Doesn't want to take medications	9 (14)
Prefers to manage alone	6 (10)
Tried medication previously and it didn't work	5 (8)
Didn't think treatment necessary/ waiting for problems to go away	4 (6)
Psychology/counselling previously didn't work	4 (6)
No motivation for treatment	4 (6)
Thinks treatment won't work	4 (6)
No time	2 (3)
Doesn't trust health professionals	2 (3)
Cost of treatment	2 (3)
Prefers to use exercise to manage	2 (3)
Culturally unacceptable to seek treatment	1 (2)
Forgets to take medication	1 (2)

Note. The percentages do not sum to 100% because participants could give multiple reasons for not being in treatment.

Table 3

Pearson's Correlations for Study Variables

Variable	1	2	3	4	5	6	7
1. Cortisol							
2. Oxytocin	0.11						
3. Psychopathology $_{\text{DASS Total}}$	.49**	-0.14					
4. Help-seeking Informal $_{\text{GHSQ}}$	-.35**	.22*	-.47**				
5. Help-seeking Formal $_{\text{GHSQ}}$	-0.02	0.02	-0.06	0.09			
6. Help-seeking All Sources $_{\text{GHSQ}}$	-.24**	.19*	-.37**	.74**	.71**		
7. Perceived Social Support $_{\text{ISEL-12}}$	0.02	0.07	-.26**	.25**	0.13	.27**	
8. Suicidal ideation $_{\text{BSI Item 9}}$	.33**	0.02	.55**	-.37**	-0.12	-.35**	-.37**

Note: DASS = Depression, Anxiety and Stress Scales; GHSQ = General Help-Seeking Questionnaire; ISEL-12 = Interpersonal Support Evaluation List-12; BSI =Brief Symptom Inventory.
*$p < .05$, **$p < .01$

Table 4

Summary of Hierarchical Multiple Regression Analyses Predicting Help-Seeking Intentions from Informal Sources

Predictor	R^2	Adjusted R^2	ΔR^2	B	SE B	β	*p*
Step 1	.23	.21	.23**				
Psychopathology $_{\text{DASS Total}}$				-.02	.01	-.35	<.01**
Suicidal ideation $_{\text{BSI Item 9}}$				-.21	.17	-.13	.20
Perceived social support $_{\text{ISEL-12}}$				.04	.03	.11	.13
Step 2	.30	.27	.07*				
Psychopathology $_{\text{DASS Total}}$				-.01	.01	-.20	.06
Suicidal ideation $_{\text{BSI Item 9}}$				-.22	.17	-.13	.20
Perceived social support $_{\text{ISEL-12}}$				.05	.03	.16	.07
Cortisol				-.003	.00	-.24	.01*
Oxytocin				.002	.00	.21	.01*

Note. SE = Standard Error, *DASS = Depression, Anxiety and Stress Scales; GHSQ = General Help-Seeking Questionnaire; ISEL-12 = Interpersonal Support Evaluation List-12; BSI =Brief Symptom Inventory.*

*$p < .05$, **$p < .01$.

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